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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/142,660	12/23/1998	RAINER HINTSCHE	60953/119	2492

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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/142,660	HINTSCHE ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25,27-34,37-40,42-55 and 59-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25,27-34,37-40,42-55 and 59-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *43* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Group 1630, Art Unit 1634.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 20 May 2002 has been entered.

Claim Objections

3. Claims 52 and 55 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 52 stipulates that the electrode structures are insulted from one another by an insulating material yet claim 21, from which claim 52 depends, already indicates that the electrode structures are insulated from one another. Claim 55 indicates that direct **OR** alternating current is to be applied yet claim 21 stipulates that an alternating

electric field is generated. Such language in claim 55 is considered to broaden, not further limit the scope of claim 21.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 21-25, 27-34, 37-40, 42-55 and 59-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for coating of an electrode with SH-biotin and detection/measurement of β-galactosidase-streptavidin wherein said β-galactosidase-streptavidin binds to the immobilized biotin and is subsequently detected by the action of β-galactosidase on ρ-aminophenol, does not reasonably provide enablement for the detection of any molecule complex in any diluent, be it in a purified state or not, and where the ultra-microelectrode array is fashioned of any material and is operated under any strength of electric field, any amplitude, and any frequency. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5)

the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary

The amount of experimentation is great, on the order of many man-years with little if any reasonable expectation of success.

The Amount of Direction or Guidance Provided and The Presence or Absence of Working Examples

The specification has been found to provide but one example where any molecule was detected and that was for the presence of β-galactosidase-streptavidin. In accordance with the example provided at pages 13-14 of the specification, SH-Biotin was first coated onto a gold electrode that had a width of 1 μm and an electrode spacing of 0.7 μm. The modified electrode was then dipped for 2 hours in a 50 U/ml solution of β-galactosidase-streptavidin and subsequently rinsed for 10 minutes in 0.1 mol/ml Na buffer solution.

As set forth at page 14, a Nyquist plot for a potential of 50 mV, amplitude of 10 mV and a frequency range of between $2x10^{-13}$ Hz and $1X10^{6}$ Hz, measured as two-pole impedance.

The specification does not set forth the conditions required to accurately detect any other molecule or molecule complex in any diluent under any set of conditions, including the detection of molecules or molecular complexes that comprise nucleic acid or antibodies (amended claim 21). The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Claim 23 requires measurement to be made via impedance spectroscopy. However, the specification does not set forth a repeatable procedure whereby this is to be conducted. The specification does not enable the application of "a direct-current component", nor the oxidation or reduction of an electrically active molecule.

Claims 28-30, while limiting of claim 21, clearly indicate that the claims are to encompass the induction of any and all possible electrochemical reactions. The specification has not set forth a sufficient number of members of the genus of electrochemical reactions so to enable the genus. While the specification need not set forth an example of each and every possible permutation encompassed by the claims, the specification does need to fully enable the complete scope of the invention. Additionally, greater levels of disclosure are required where the invention is drawn to an inherently unpredictable area, such as the chemical and physiological arts; see *In re Fisher* 166 USPQ 18, 24 (CCPA 1970) and *In re Shokal*, 113 USPQ 283 (CCPA 1957). Similarly, the specification does not set forth a repeatable procedure where the molecule to be detected is an antibody (claim 40), nor for when the first and or second molecules comprise polynucleotides (claims 42-44). The specification has not been found to set forth a repeatable procedure whereby one of skill in the art would be able to synthesize and use an electrode fashioned of a material other than gold. The limited guidance has not been found to be sufficient to enable the full scope of the claimed invention.

The Nature of the Invention

The invention relates to the detection of virtually any molecule or molecular complex, be it in a purified or heterogeneous mixture, and regardless of concentration. The claimed method employs an alternating electrical current and the skilled artisan is to measure changes in current or in electrical potential between electrode structures, which are to be interpreted as being indicative of a molecule or molecular complex. While independent claim 21 recites the limitation that the "molecule or molecular complex comprises a nucleic acid or antibody," the

claim does not necessarily require that the detection be that of the nucleic acid or antibody, but rather, the detection could be directed to some other aspect or molecule that is present. The specification, as set forth above, is essentially silent as to how any such molecule is to be detected.

Claim 33 requires the molecules or molecular complex bind to the surface via "self-assembling." The specification, however, is essentially silent as to how a nucleic acid and/or antibody is to undergo self-assembly under any condition, much les in the context of the claimed assay.

The State of the Prior Art

The state of the prior art in this area is relatively undeveloped, especially when one is attempting to detect any type of molecule or molecular complex, be it in a purified or heterogeneous mixture of varying concentrations, buffers, temperatures, etc.

The Relative Skill of Those in the Art

The relative skill of those in the art most closely related to the claimed invention is high, on par with those who hold a Ph.D. in biochemistry and have a firm grounding on electrical chemistries.

Breadth of the claims

The claims have sufficient breadth of scope so to encompass the detection and identification of one or more molecules at a time. The claims also have sufficient breadth of scope so to encompass the use of electrodes that are in contact with one another as well as those that are

separated by a subatomic distance. Support for this interpretation is based in part on the limitation whereby the electrodes are to be spaced "less than 3 μm" apart (claims 21-24, 27-34, 37-40, 42-55, 59-60 and 62) or be spaced "less than 1 μm" apart (claim 61).

In view of the limited disclosure, the unpredictableness of he art to which the invention relates, and the breadth of scope encompassed by the claims, the specification has not been found to fully enable the claimed invention. Accordingly, the claims have been rejected under 35 USC 112, first paragraph, as it relates to matters of scope of enablement. Applicant I again urged to consider narrowing the scope of the claims to those embodiments for which adequate enabling disclosure exists.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 21-25, 27-34, 37-40, 42-55 and 59-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 21 is indefinite with respect to the use of "molecule complex" in line 1 and the use of "molecular complex" in lines 3 and 12. Claim 21 is confusing where in step (c) there appears "is position in the gap." Perhaps applicant had intended to state –is positioned in the gap--.

9. Claims 22 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: that which will result in the detection of "a molecule" in a sample that comprises any number of non-target molecules or non-target

molecular complexes. As presently worded, the claimed method is to result in the detection of "a molecule or molecular complex in a sample." The claim places no restriction on the heterogeneity of the sample and as such, the claims have been interpreted as encompassing highly heterogeneous samples wherein said samples comprise an overwhelming majority of non-target molecules/molecular complexes and a minute amount of target or even no target molecules. As presently worded, all one needs to perform is monitor a change in current and/or impedance. However, simply monitoring current and/or impedance will not necessarily result in the detection of any molecule or molecular complex. Applicant is urged to consider amending the claims such that the recited method steps will actually result in the intended product, and the intended product being that found in the preamble of the claim- the detection of a molecule or molecular complex. Claims 22-25, 27-34, 37-40, 42-55, 59-60 and 62, which depend from said claim 21, fail to overcome this issue and are similarly rejected.

10. Claim 22 is confusing as to how an "insulating support material" acts to uncover "an insulating support material."

11. Claim 22 is confusing where it is stated "in the direction of the measurement." It is unclear how "measurement" has direction.

12. Claim 23 provides for the use of impedance spectroscopy, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

13. Claim 23 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e.,

results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

14. Claim 33 is confusing as to how one is to monitor "self-assembly" of a nucleic acid or of an antibody.

15. Claim 37 is confusing as to the usage of "which." In particular, is "which" in reference to the electrode structures or in reference to the "substrate?"

16. Claim 38 is confusing wherein is stated: "contacts with a surface."

17. Claims 39, 40, 42 and 44 lack antecedent support for "the second molecule."

18. Claim 43 lacks antecedent support for "the second polynucleotide."

19. Claim 44 lacks antecedent support for "the first, second and third polynucleotides."

20. Claim 51 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: between the various electrode structures, the gap, the insulating material, etc., when the electrode structures are to be in the form of an "ultra-microelectrode array" and yet be in the configuration of "a band structure, a strip structure, a circular structure or a finger-like interdigital structure."

Claim Rejections - 35 USC § 103

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 21-25, 27-34, 37-40, 42-55 and 59-62 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hollis et al. (US Patent 5,653,939).

26. Hollis et al., teach at length devices and method for electrical detection of molecules, including that of nucleic acids. As seen in Figure 3, Figure 4, and column 6, the device can comprise channels that are 2 microns wide and are 0.5 microns deep. In Figure 1 there is disclosed and depicted layers of such channels crossing over one another and wherein the electrodes found within each channel are insulated from other electrodes at the cross-over point.

27. Support surfaces are disclosed at column 11.

28. The utilization of the device for where proteins are bound is disclosed at column 12. Table III, column 18, specifically recites the use of antibodies.

29. In view of the teachings of the prior art of record, the invention set forth in claims 21-25, 27-34, 37-40, 42-55 and 59-62 is anticipated by, or I the alternative, rendered obvious by the disclosure of Hollis et al.

Conclusion

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

32. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
August 6, 2002